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(54) Title: 9-OXA PROSTAGLANDIN ANALOGS AS OCULAR HYPOTENSIVES

(57) Abstract

Substritued tetrahydrofuran analogs of prostaglandins and methods of their use in treating glaucoma and ocular hypertension are disclosed.

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9-OXA PROSTAGLANDIN ANALOGS AS OCULAR HYPOTENSIVES

Background of the Invention

The present invention relates to novel compounds and compositions, and methods of their use in the treatment of glaucoma and ocular hypertension. In particular, the present invention relates to the use of certain substituted tetrahydrofuran analogs of D and F series prostaglandins to treat glaucoma and ocular hypertension.

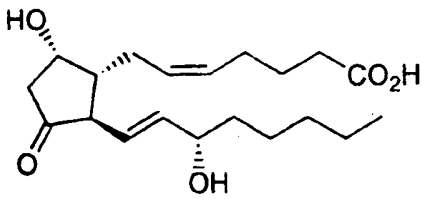
Glaucoma is a progressive disease which leads to optic nerve damage, and, ultimately, total loss of vision. The causes of this disease have been the subject of extensive studies for many years, but are still not fully understood. The principal symptom of and/or risk factor for the disease is elevated intraocular pressure or ocular hypertension due to excess aqueous humor in the anterior chamber of the eye.

The causes of aqueous humor accumulation in the anterior chamber are not fully understood. It is known that elevated intraocular pressure ("IOP") can be at least partially controlled by administering drugs which reduce either the production of aqueous humor within the eye, such as beta-blockers and carbonic anhydrase inhibitors, or increase the flow of aqueous humor out of the eye, such as miotics and sympathomimetics.

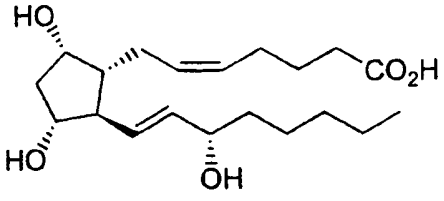
Most types of drugs conventionally used to treat glaucoma have potentially serious side effects. Miotics such as pilocarpine can cause blurring of vision and other visual side effects, which may lead either to decreased patient compliance or to termination of therapy. Systemically administered carbonic anhydrase inhibitors can also cause serious side effects, such as nausea, dyspepsia, fatigue, and metabolic acidosis, which side effects can affect patient compliance and/or necessitate the termination of treatment. Another type of drug, beta-blockers, have increasingly become associated with serious pulmonary side effects attributable to their effects on beta-2 receptors in pulmonary tissue. Sympathomimetics may cause tachycardia, arrhythmia and hypertension. There is

therefore a continuing need for therapies which control the elevated intraocular pressure associated with glaucoma.

Prostaglandins, which are metabolite derivatives of arachidonic acid, have recently been pursued for possible efficacy in lowering IOP. Arachidonic acid in the body is converted to prostaglandin G_2, which is subsequently converted to prostaglandin H_2. Other naturally occurring prostaglandins are derivatives of prostaglandin H_2. A number of different types of prostaglandins have been discovered including A, B, D, E, F, G, I and J-series prostaglandins (EP 0 561 073 A1). Of interest in the present invention are compounds which are believed to exhibit IOP lowering mechanisms similar to those exhibited by PGD_2 (formula **I**) and $PGF_{2\alpha}$ (formula **II**):



I



II

The relationship between prostaglandin DP receptor activation and IOP lowering effects is not well understood. Various publications have reported that DP receptor activation leads to second messenger activation and in particular, to the stimulation of adenylate cyclase and resultant increases in cAMP levels (Thierauch, *Prostaglandins and their Receptors: II. Receptor Structure and Signal Transduction*, Journal of Hypertension, volume 12, pages 1-5 (1994). Regardless of mechanism, PGD_2 has been shown to lower IOP (Nakajima, *Effects of Prostaglandin D_2 and its analog, BW245C, on Intraocular Pressure in Humans*, Graefe's Archive Ophthalmology, volume 229, pages 411-413 (1991)). Thus, it has been of interest in the field to develop synthetic PGD_2 analogs with IOP lowering efficacy.

Synthetic PGD_2-type analogs have been pursued in the art (Graefe's Archive Ophthalmology, volume 229, pages 411-413 (1991)). Though some PGD_2-type molecules

lower IOP, these types of molecules have also been associated with undesirable side effects resulting from topical ophthalmic dosing. Such effects have included an initial increase in IOP, conjunctival hyperemia, increases in microvascular permeability, and increases in eosinophile infiltration (Alm, *The Potential of Prostaglandin Derivatives in Glaucoma Therapy*, Current Opinion in Ophthalmology, volume 4, No. 11, pages 44-50 (1993)).

Similarly, the relationship of prostaglandin FP receptor activation and IOP lowering effects is not well understood. It is believed that FP receptor activation leads to increased outflow of aqueous humor. Regardless of mechanism, $PGF_{2\alpha}$ and some of its analogs have been shown to lower IOP (Giuffre, *The Effects of Prostaglandin $F_{2\alpha}$ the Human Eye*, Graefe's Archive Ophthalmology, volume 222, pages 139-141 (1985); and Kerstetter et al., *Prostaglandin $F_{2\alpha}$-1-Isopropylester Lowers Intraocular Pressure Without Decreasing Aqueous Humor Flow*, American Journal of Ophthalmology, volume 105, pages 30-34 (1988)). Thus, it has been of interest in the field to develop synthetic $PGF_{2\alpha}$ analogs with IOP lowering efficacy.

Synthetic $PGF_{2\alpha}$-type analogs have been pursued in the art (Graefe's Archive Ophthalmology, volume 229, pages 411-413 (1991)). Though $PGF_{2\alpha}$-type molecules may lower IOP, these types of molecules have also been associated with undesirable side effects resulting from topical ophthalmic dosing. Such effects include an initial increase in IOP, breakdown of the blood aqueous barrier and conjunctival hyperemia (Alm, *The Potential of Prostaglandin Derivatives in Glaucoma Therapy*, Current Opinion in Ophthalmology, volume 4, No. 11, pages 44-50 (1993)).

Based on the foregoing, a need exists for the development of molecules that may activate the prostaglandin DP and/or FP receptors, yielding a more efficacious lowering of IOP, while exhibiting fewer or reduced side effects.

An agent which exhibits comparable or improved efficacy, but with reduced side effects when compared to other agents, is said to have an improved therapeutic profile. It

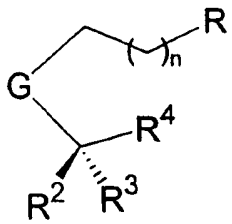
is an object of this invention to provide a class of IOP lowering agents with an improved therapeutic profile over endogenous prostaglandins, and methods of their use.

Summary of the Invention

The present invention is directed to compositions and methods of their use in treating glaucoma and ocular hypertension. In particular, the present invention provides certain classes of substituted tetrahydrofurans which may possess functional DP and/or FP receptor agonist activity, and methods of their use in treating glaucoma and ocular hypertension.

Detailed Description of the Invention

It has unexpectedly been found that substituted tetrahydrofurans of the present invention exhibit an improved therapeutic profile in the treatment of glaucoma and ocular hypertension when compared to natural prostaglandins and many of their known analogs. The substituted tetrahydrofurans of the present invention are heptanoic acid derivatives having the following formula (**III**):



III

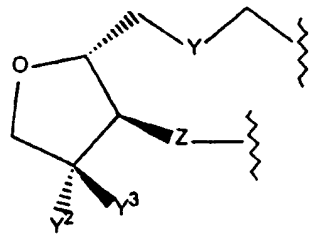
wherein:

R = ophthalmically acceptable ester moiety, CO_2R^1, $CONR^7R^8$, CH_2OR^9, or $CH_2NR^{10}R^{11}$, where R^1 = H, a cationic salt moiety, or an ophthalmically acceptable ammonium moiety; R^7 and R^8 are the same or different = H or alkyl; R^9 = H, acyl, or alkyl; and

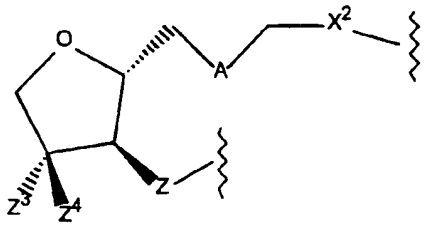
R^{10} and R^{11} are the same or different = H, acyl, or alkyl; with the proviso that if one of R^{10} and R^{11} = acyl, then the other = H or alkyl;

n = 0 or 2;

G is:

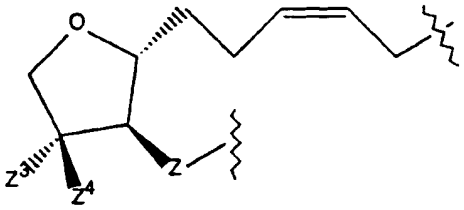


(i)



(ii)

or



(iii)

wherein:

Y = *cis* $CH_2CH=CH$, *cis* $CH=CHCH_2$, or $CH_2CH_2CH_2$;

Z = C≡C, *trans* CH=CH, or CH_2CH_2;

one of Y^2 and Y^3 = H, and the other = halogen or OH, where the OH may be free or functionally modified;

X^2 = O, S, or CH_2;

A = *cis* CH=CH, CH_2CH_2, or C≡C ; and

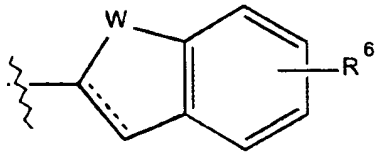
one of Z^3 and Z^4 = H, and the other = OH, where the OH may be free or functionally modified; or Z^3 and Z^4 taken together = double bonded O (carbonyl);

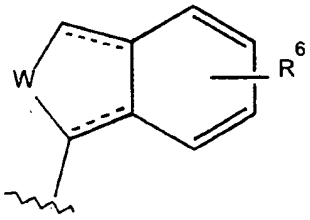
one of R^2 and R^3 = H, and the other = F or OH, where the OH may be free or functionally modified; or R^2 and R^3 taken together = OCH_2CH_2O or double bonded O (carbonyl); and

R^4 = cyclohexyl, linear or branched C_5-C_7 alkyl, or R^5, wherein:

R^5 = $(CH_2)_m$Xphenyl or $(CH_2)_p$ Z^2, where X = O or CH_2; m = 1-6; the phenyl is either unsubstituted or substituted with R^6, where R^6 = halogen, CH_3, CF_3, CN, OCH_3 or acetyl; p = 0-6; and

Z^2 =





or

wherein:

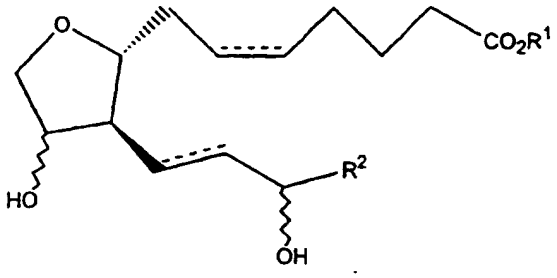
W = O, CH_2, CH_2CH_2, or CH=CH; and R^6 is as defined above;

provided that when G is **(i)** then R^4 = R^5; and when G is **(ii)** or **(iii)** then R^4 = cyclohexyl, linear or branched C_5-C_7 alkyl, and R^2, R^3 are different = H and OH.

For purposes of the foregoing definition, the terms "ophthalmically acceptable ester moiety" and "ophthalmically acceptable ammonium moiety" mean any ester or ammonium moiety that would be suitable for ophthalmic application, i.e. non-toxic and non-irritating. Preferred esters are alkyl and alkylcycloalkyl esters of carboxylic acids. Most preferred are C_2-C_5 alkyl esters of carboxylic acids, and especially isopropyl esters.

With the exception of compounds represented by formulas **IV** and **V** depicted below, racemic systheses of which have been reported by Vlattas, I. in U.S. Patents

3,883,659 and 4,088,779, and Vlattas, et al., Tetrahedron Letters, 4455-4458 (1974), the compounds useful in the present invention are believed to be novel.

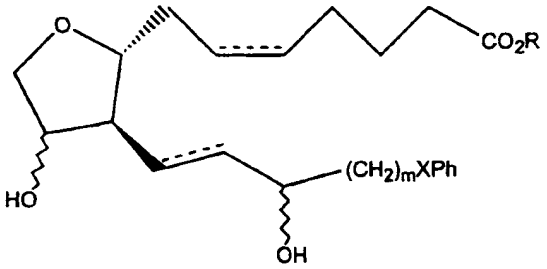


IV

wherein:

R^1 = H; alkali metal, or lower alkyl; and

R^2 = cyclohexyl; lower alkyl.



V

wherein:

R = H, alkali metal, or lower alkyl;

phenyl is either unsubstituted or substituted with halogen, CF_3, lower alkoxy, lower alkyl;

m = 1-4; and

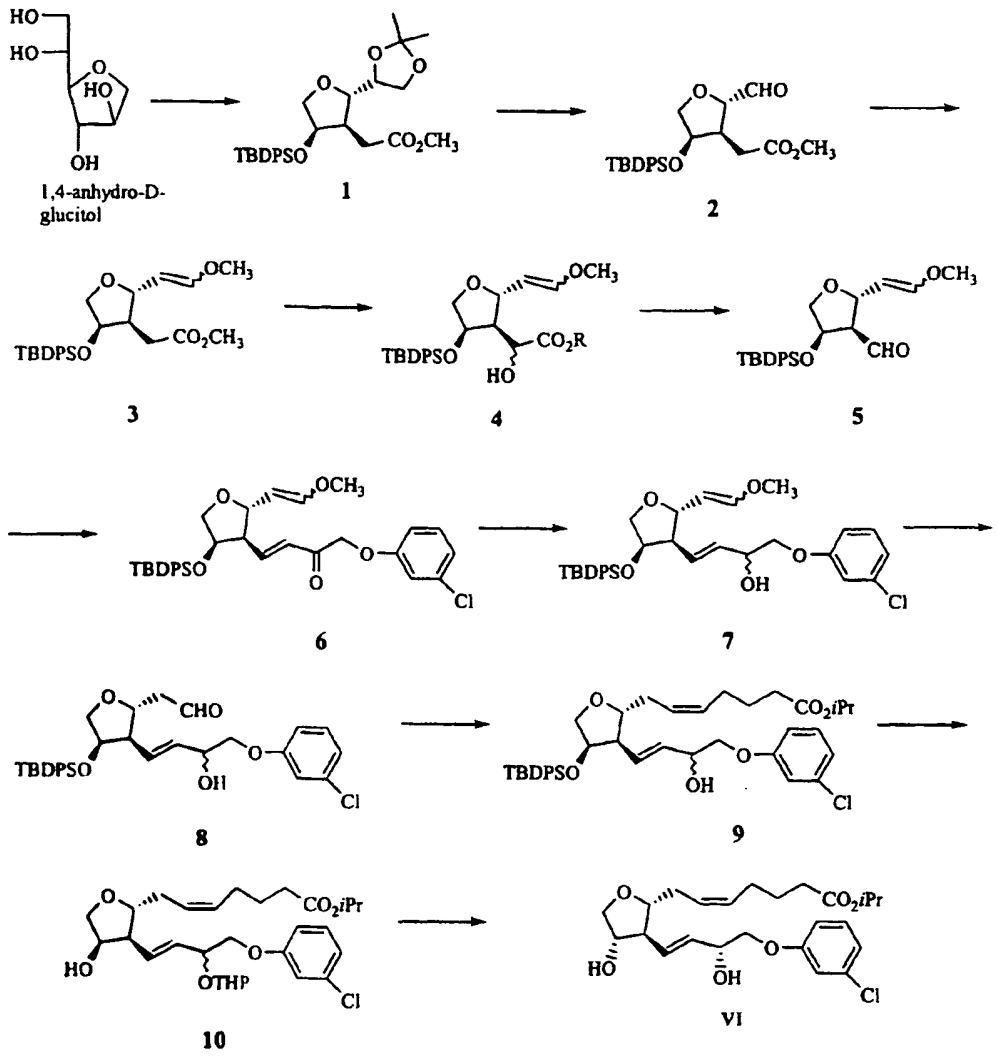
X = CH_2 or O.

In the foregoing illustrations, as well as those provided hereinafter, wavy line attachments indicate that the configuration may be either alpha (α) or beta (β). The dashed lines on bonds between carbons, e.g. in the bicyclic structural formula for Z^2, indicate a single or double bond. Two solid lines present between carbons specify the configuration of the relevant double bond. Hatched lines indicate the α configuration, and a solid triangular line indicates the β configuration.

EXAMPLE 1: SYNTHESIS OF Isopropyl [2*R*(5*Z*),3*S*(1*E*,3*R*),4*S*]-7-[Tetrahydro-3-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-2-furanyl]-5-heptenoate (VI).

Compound **VI** may be prepared according to the synthetic route outlined in the following Scheme. The intermediate **1** is prepared from the chiral starting material 1,4-anhydro-D-glucitol, according to the methodology described in Hanessian, et al., Carbohydrate Research, 141:221-238 (1985); 1,4-anhydro-D-glucitol itself is conveniently prepared following the procedure of Bock, K. et al., Acta Chemica Scandinavica B, 35:441-449 (1981).

Scheme: A Synthetic Route for the Preparation of Compound VI



Treatment of compound 1 with HIO_4 affords the aldehyde 2 which is then homologated under Wittig reaction conditions to afford the enolether 3. The ester 3 is then reacted with potassium hexamethyldisilazide in THF, and the ester enolate thus formed is quenched with 2-phenylsulfonyl-3-phenyloxaziridine to afford the α-hydroxy methyl ester 4 (R = CH_3). Conversion of the ester to the α-hydroxy acid 4 (R = H) and reaction of this intermediate carboxylic acid with tetra-n-butylammonium periodate affords the aldehyde

5. Horner-Emmons reaction of **5** with dimethyl-3-(3-chlorophenoxy)-2-oxopropyl-phosphonate affords the enone **6**. Reduction of **6** with sodium borohydride in the presence of cerium chloride afford the allylic alcohol **7**. Deprotection of the enol ether functionality in **7** under mildly acidic conditions, reaction of the resulting intermediate aldehyde **8** with the ylid derived from (4-carboxybutyl)triphenylphosphonium bromide affords the crude carboxylic acid which is then esterified to the isopropyl ester **9**. Protection of the allylic alcohol in **9** as the THP ether, deprotection of the silyl ether with tetrabutylammonium fluoride affords the alcohol **10**. Oxidation and reduction of this alcohol function and deprotection of the THP ether under acidic conditions followed by separation of the diastereomers by silica chromatography affords compound **VI**.

The substituted tetrahydrofurans of the present invention may be formulated in various pharmaceutical compositions for administering to humans and other mammals as a treatment of glaucoma or ocular hypertension. As used herein, the term "pharmaceutically effective amount" refers to that amount of a compound of the present invention which lowers IOP when administered to a patient, especially a mammal. The preferred route of administration is topical. The compounds of the present invention can be administered as solutions, suspensions, or emulsions (dispersions) in an ophthalmically acceptable vehicle. As used herein, the term "ophthalmically acceptable vehicle" refers to any substance or combination of substances which are non-reactive with the compounds and suitable for administration to a patient. Solubilizers and stabilizers are deemed to be non-reactive. Preferred are aqueous vehicles suitable for topical application to the patient's eyes.

In forming compositions for topical administration, the compounds of the present invention are generally formulated as between about 0.00003 to about 0.5 percent by weight (wt%) solutions in water at a pH between about 4.5 to about 8.0, preferably between about 5.0 and about 7.5. The compounds are preferably formulated as between about 0.0005 to about 0.03 wt% and, most preferably, between about 0.001 and about 0.01 wt%. While the precise regimen is left to the discretion of the clinician, it is recommended that the resulting solution be topically applied by placing one drop in each eye one or two times a day.

Other ingredients which may be desirable to use in the ophthalmic preparations of the present invention include preservatives, co-solvents, and viscosity building agents.

Antimicrobial Preservatives:

Ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other agents known to those skilled in the art. Such preservatives are typically employed at a level between about 0.001% and about 1.0% by weight.

Co-Solvents:

Prostaglandins, and particularly ester derivatives, typically have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: Polysorbate 20, 60 and 80; Pluronic F-68, F-84 and P-103; CREMOPHORE® EL (polyoxyl 35 castor oil); cyclodextrin; or other agents known to those skilled in the art. Such co-solvents are typically employed at a level between about 0.01% and about 2% by weight.

Viscosity Agents:

Viscosity greater than that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the ophthalmic formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, chondroitin sulfate and salts thereof, hyaluronic acid

and salts thereof, and other agents known to those skilled in the art. Such agents are typically employed at a level between about 0.01% and about 2% by weight.

Preferred formulations of substituted tetrahydrofurans of the present invention include the following Example 2:

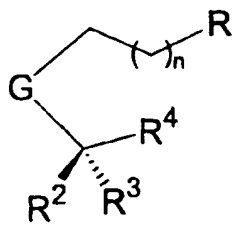
Example 2

Ingredient	Amount (wt%)
Compound **VI**	0.01
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA (Edetate disodium)	0.05
Cremophor® EL	0.1
Benzalkonium chloride	0.01
HCl and/or NaOH	q.s. pH 7.3 - 7.4
Purified water	q.s. 100%

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is claimed is:

1. A method of treating glaucoma or ocular hypertension in a patient, which comprises administering to the patient a pharmaceutically effective amount of a compound of the formula following **III**:



III

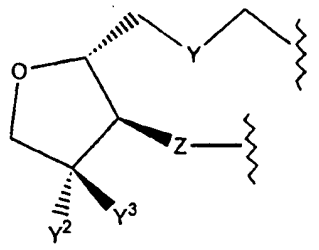
wherein:

R = ophthalmically acceptable ester moiety, CO_2R^1, $CONR^7R^8$, CH_2OR^9, or $CH_2NR^{10}R^{11}$

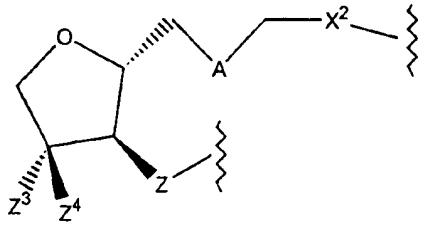
where R^1 = H, a cationic salt moiety, or an ophthalmically acceptable ammonium moiety; R^7 and R^8 are the same or different = H or alkyl; R^9 = H, acyl, or alkyl; and R^{10} and R^{11} are the same or different = H, acyl, or alkyl; with the proviso that if one of R^{10} and R^{11} = acyl, then the other = H or alkyl;

n = 0 or 2;

G is:

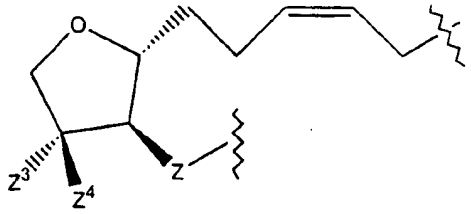


(i)



(ii)

or



(iii)

wherein:

Y = *cis* $CH_2CH=CH$, *cis* $CH=CHCH_2$, or $CH_2CH_2CH_2$;

Z = C≡C, *trans* CH=CH, or CH_2CH_2;

one of Y^2 and Y^3 = H, and the other = halogen or OH, where the OH may be free or functionally modified;

X^2 = O, S, or CH_2;

A = *cis* CH=CH, CH_2CH_2, or C≡C ; and

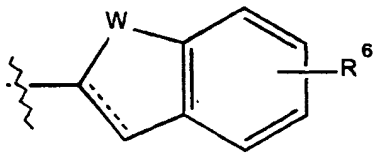
one of Z^3 and Z^4 = H, and the other = OH, where the OH may be free or functionally modified; or Z^3 and Z^4 taken together = double bonded O (carbonyl);

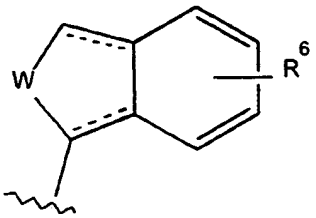
one of R^2 and R^3 = H, and the other = F or OH, where the OH may be free or functionally modified; or R^2 and R^3 taken together = OCH_2CH_2O or double bonded O (carbonyl); and

R^4 = cyclohexyl, linear or branched C_5-C_7 alkyl, or R^5, wherein:

$R^5 = (CH_2)_m$Xphenyl or $(CH_2)_p Z^2$, where X = O or CH_2; m = 1-6; the phenyl is either unsubstituted or substituted with R^6, where R^6 = halogen, CH_3, CF_3, CN, OCH_3 or acetyl; p = 0-6; and

Z^2 =





or

wherein:

W = O, CH_2, CH_2CH_2, or CH=CH; and R^6 is as defined above;

provided that when G is **(i)** then $R^4 = R^5$, and when G is **(ii)** or **(iii)** then R^4 = cyclohexyl, linear or branched C_5-C_7 alkyl, and R^2, R^3 are different = H, and OH.

2. The method of claim 1, where the compound is administered topically.

3. The method of claim 2, wherein the compound is administered as a solution, suspension, or emulsion.

4. The method of claim 2, wherein G is **(i)**.

5. The method of claim 2, wherein G is **(ii)**

6. The method of claim 2, wherein G is **(iii)**.

7. The method of claim 4, wherein R is an ophthalmically acceptable ester selected from the group consisting of: isopropyl and neopentyl esters of carboxylic acids.

8. The method of claim 5, wherein R is an ophthalmically acceptable ester selected from the group consisting of: isopropyl and neopentyl esters of carboxylic acids, and R^4 is cyclohexyl.

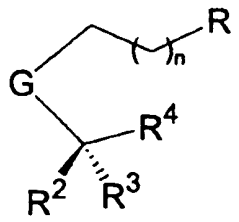
9. The method of claim 6, wherein R is an ophthalmically acceptable ester selected from the group consisting of: isopropyl and neopentyl esters of carboxylic acids, and R^4 is cyclohexyl.

10. The method of claim 3, wherein the concentration of the compound is between about 0.00003 to about 0.5 weight percent.

11. The method of claim 10, wherein the concentration of the compound is between about 0.0005 to about 0.03 weight percent.

12. The method of claim 11, wherein the concentration of the compound is between about 0.001 and about 0.01 weight percent.

13. A compound of the following formula **III**:



III

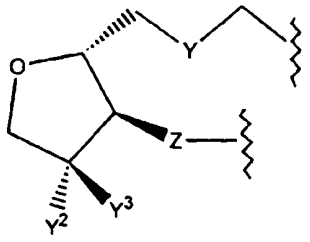
wherein:

R = ophthalmically acceptable ester moiety, CO_2R^1, $CONR^7R^8$, CH_2OR^9, or $CH_2NR^{10}R^{11}$

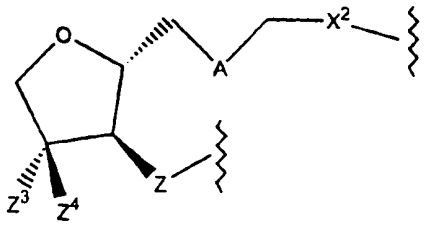
where R^1 = H, a cationic salt moiety, or an ophthalmically acceptable ammonium moiety; R^7 and R^8 are the same or different = H or alkyl; R^9 = H, acyl, or alkyl; and R^{10} and R^{11} are the same or different = H, acyl, or alkyl; with the proviso that if one of R^{10} and R^{11} = acyl, then the other = H or alkyl;

n = 0 or 2;

G is:

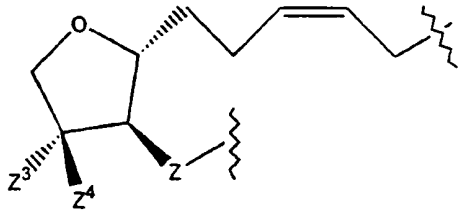


(i)



(ii)

or



(iii)

wherein:

Y = *cis* $CH_2CH=CH$, *cis* $CH=CHCH_2$, or $CH_2CH_2CH_2$;

Z = C≡C, *trans* CH=CH, or CH_2CH_2;

one of Y^2 and Y^3 = H, and the other = halogen or OH, where the OH may be free or functionally modified;

X^2 = O, S, or CH_2;

A = *cis* CH=CH, CH_2CH_2, or C≡C ; and

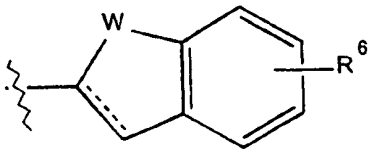
one of Z^3 and Z^4 = H, and the other = OH, where the OH may be free or functionally modified; or Z^3 and Z^4 taken together = double bonded O (carbonyl);

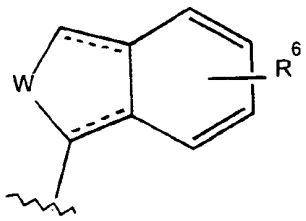
one of R^2 and R^3 = H, and the other = F or OH, where the OH may be free or functionally modified; or R^2 and R^3 taken together = OCH_2CH_2O or double bonded O (carbonyl); and

R^4 = cyclohexyl, linear or branched C_5-C_7 alkyl, or R^5, wherein:

R^5 = $(CH_2)_m$Xphenyl or $(CH_2)_p$ Z^2, where X = O or CH_2; m = 1-6; the phenyl is either unsubstituted or substituted with R^6, where R^6 = halogen, CH_3, CF_3, CN, OCH_3 or acetyl; p = 0-6; and

Z^2 =





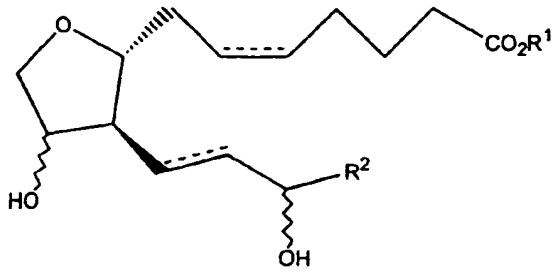
or

wherein:

W = O, CH_2, CH_2CH_2, or CH=CH; and R^6 is as defined above;

provided that when G is **(i)** then $R^4 = R^5$, and when G is **(ii)** or **(iii)** then R^4 = cyclohexyl, linear or branched C_5-C_7 alkyl, and R^2, R^3 are different = H, and OH;

and further provided that the compounds of the following formulas **IV** and **V** be excluded:

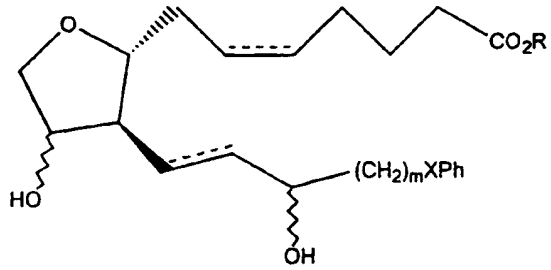


IV

wherein:

R^1 = H; alkali metal, or lower alkyl

R^2 = cyclohexyl; lower alkyl; and



V

wherein:

R = H, alkali metal, or lower alkyl

phenyl is either unsubstituted or substituted with halogen, CF_3, lower alkoxy, lower alkyl

m = 1-4

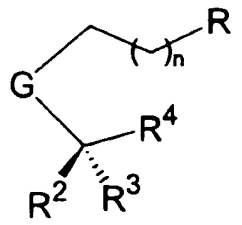
$X = CH_2$ or O.

14. The compound of claim 13, where G is **(i)**.

15. The compound of claim 13, where G is **(ii)**.

16. The compound of claim 13, wherein G is **(iii)**.

17. An ophthalmic composition for the treatment of glaucoma and ocular hypertension, comprising a compound of formula **III**:



III

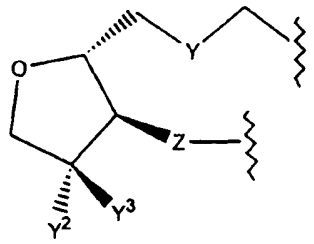
wherein:

R = ophthalmically acceptable ester moiety, CO_2R^1, $CONR^7R^8$, CH_2OR^9, or $CH_2NR^{10}R^{11}$.

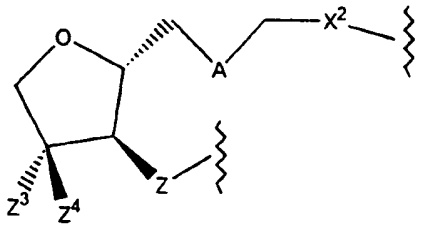
where R^1 = H, a cationic salt moiety, or an ophthalmically acceptable ammonium moiety; R^7 and R^8 are the same or different = H or alkyl; R^9 = H, acyl, or alkyl; and R^{10} and R^{11} are the same or different = H, acyl, or alkyl; with the proviso that if one of R^{10} and R^{11} = acyl, then the other = H or alkyl;

n = 0 or 2;

G is:

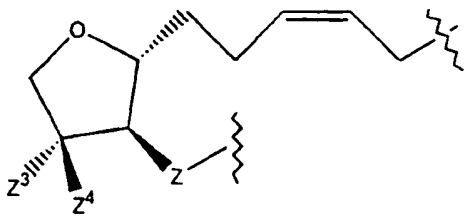


(i)



(ii)

or



(iii)

wherein:

Y = *cis* $CH_2CH=CH$, *cis* $CH=CHCH_2$, or $CH_2CH_2CH_2$;

Z = C≡C, *trans* CH=CH, or CH_2CH_2;

one of Y^2 and Y^3 = H, and the other = halogen or OH, where the OH may be free or functionally modified;

X^2 = O, S, or CH_2;

A = *cis* CH=CH, CH_2CH_2, or C≡C ; and

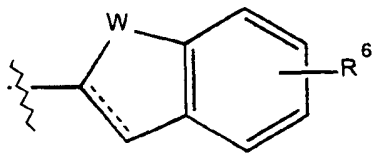
one of Z^3 and Z^4 = H, and the other = OH, where the OH may be free or functionally modified; or Z^3 and Z^4 taken together = double bonded O (carbonyl);

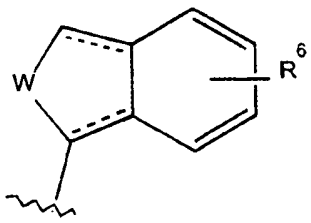
one of R^2 and R^3 = H, and the other = F or OH, where the OH may be free or functionally modified; or R^2 and R^3 taken together = OCH_2CH_2O or double bonded O (carbonyl); and

R^4 = cyclohexyl, linear or branched C_5-C_7 alkyl, or R^5, wherein:

$R^5 = (CH_2)_mX$phenyl or $(CH_2)_p Z^2$, where X = O or CH_2; m = 1-6; the phenyl is either unsubstituted or substituted with R^6, where R^6 = halogen, CH_3, CF_3, CN, OCH_3 or acetyl; p = 0-6; and

Z^2 =





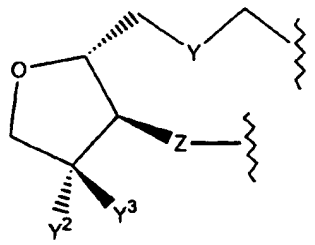
or

wherein:

W = O, CH_2, CH_2CH_2, or CH=CH; and R^6 is as defined above;

provided that when G is **(i)** then $R^4 = R^5$; and when G is **(ii)** or **(iii)** then R^4 = cyclohexyl, linear or branched C_5-C_7 alkyl, and R^2, R^3 are different = H, and OH;
and pharmaceutically acceptable salts thereof; and an ophthalmically acceptable vehicle therefor.

18. The composition of claim 17, where G is:

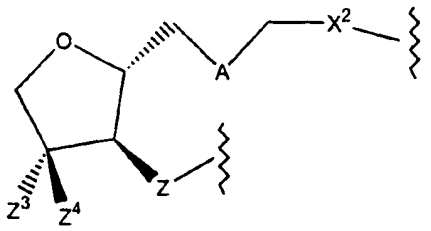


(i)

Y = *cis* CH_2CH=CH, *cis* CH=$CHCH_2$, or $CH_2CH_2CH_2$;
Z = C≡C, *trans* CH=CH, or CH_2CH_2;
one of Y^2 and Y^3 = H, and the other = halogen or OH, where the OH may be free or functionally modified;

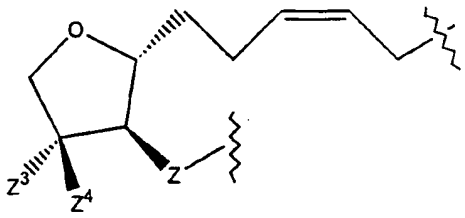
and pharmaceutically acceptable salts thereof; and an ophthalmically acceptable vehicle therefor.

19. The composition of claim 17, wherein G is:



(ii)

or



(iii)

wherein:

X^2 = O, S, or CH_2;

A = *cis* CH=CH, CH_2CH_2, or C≡C ;

one of Z^3 and Z^4 = H, and the other = OH, where the OH may be free or functionally modified; or Z^3 and Z^4 taken together = double bonded O (carbonyl);

Z = C≡C, *trans* CH=CH, or CH_2CH_2;

and pharmaceutically acceptable salts thereof; and an ophthalmically acceptable vehicle therefor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/11339

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C070307/20 A61K31/557

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 10407 A (ALCON LABORATORIES) 11 April 1996 see pages 20/1 and 25, compound IV; example 5C; claims ---	1-19
A	US 4 088 779 A (I. VLATTAS) 9 May 1978 cited in the application see claims; examples & US 3 883 659 A cited in the application -----	13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
27 October 1998	04/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Amsterdam, L

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 11339

Box I Observations where certain claims w re found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-12
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 1-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/11339

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9610407 A	11-04-1996	US 5698733 A	16-12-1997
		AU 3639895 A	26-04-1996
		EP 0783308 A	16-07-1997
		JP 10506893 T	07-07-1998
		WO 9821180 A	22-05-1998
US 4088779 A	09-05-1978	US 3883659 A	13-05-1975